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Aguilar, Cristian

2021-02

Aguilar , C , Carbajal , T , Beltran , B E , Segura , P , Muhammad , S & Choque-Velasquez , J 2021 , ' Cerebral embolization associated with parenchymal seeding of the left atrial myxoma : Potential role of interleukin-6 and matrix metalloproteinases ' , Neuropathology , vol. 41 , no. 1 , pp. 49-57 . <https://doi.org/10.1111/neup.12697>

<http://hdl.handle.net/10138/333494>

<https://doi.org/10.1111/neup.12697>

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Case Report

Cerebral embolization associated with parenchymal seeding of the left atrial myxoma: Potential role of interleukin-6 and matrix metalloproteinases

Cristian Aguilar,^{1,2}  Tomas Carbajal,¹ Brady E. Beltran,³  Pedro Segura,⁴  Sajjad Muhammad^{5,6} and Joham Choque-Velasquez⁵ 

Departments of ¹Pathology, ³Radiation Oncology, ⁴Cardiology, Edgardo Rebagliati Martins National Hospital, ²Laboratory of Pathology, National Cardiovascular Institute, Lima, Peru, ⁵Department of Neurosurgery, Helsinki University Hospital, Helsinki, Finland and ⁶Department of Neurosurgery, Medical Faculty, Heinrich-Heine-University, Düsseldorf, Germany

Systemic embolization has been reported in up to 40% of patients with left atrial myxoma, half of them with cerebral involvement. However, development of intracerebral embolization associated with parenchymal seeding of the myxoma emboli is an extremely rare complication, with only 36 histologically diagnosed cases reported in the published literature. We describe a 69-year-old woman who arrived at the emergency service with hemiparesis associated with drug-resistant epilepsy and a medical history of resection of a left atrial myxoma 10 months previously. Cranial computed tomography revealed multiple large lesions of heterogeneous density and cystic components in the occipital lobes and posterior fossa parenchyma. Histopathological analyses after stereotactic biopsy of the occipital lesion revealed infiltrative myxoma cells with benign histological findings and uniform expression of calretinin similar to that of the primary cardiac myxoma. Additional immunohistochemical studies confirmed brain parenchymal seeding of the myxoma cells with strong expression of interleukin-6 (IL-6) and focal expression of matrix metalloproteinases-2 (MMP-2). Here, we discuss the clinicopathological features of intracerebral embolization of left atrial myxomas associated with progressive parenchymal seeding of the tumor emboli and the potential pathogenic role of IL-6 and MMPs.

Key words: left atrial myxoma, embolus, interleukin-6, MMP-2, MMP-9.

INTRODUCTION

Cardiac myxoma is the most frequent primary cardiac tumor and comprises approximately 70% of primary neoplasms in the heart.¹ Clinically, cardiac myxoma has a wide presentation, ranging from constitutional symptoms to occlusive or embolic events.² Within this broad clinical spectrum, embolic events represent the hazardous manifestation of the disease, and are usually caused by tumor fragments or even complete detachment of the tumor.^{3–6}

Systemic embolization occurs in approximately 30–40% of patients with cardiac myxoma.^{7,8} As 75–80% of the tumors arise in the left atrium, approximately half of the embolic events may affect the central nervous system (CNS).⁹ The neurological manifestation of cerebral embolization depends on whether embolic tumor cells remain intraluminal, leading to ischemic stroke, invade the vessel wall, resulting in intracranial aneurysms, or, in rare circumstances, transgress the vessel wall, leading to brain parenchymal seeding.¹⁰

Factors related to the intracranial dissemination of left cardiac myxomas remain unidentified.¹¹ Some studies suggest a positive correlation between interleukin-6 (IL-6), matrix metalloproteinase (MMP)-2, and MMP-9, and increased risk of embolic events and intracranial aneurysms in left cardiac myxoma patients.^{12–14} However, the role of MMPs and IL-6 in the parenchymal seeding of the tumor emboli remains unknown.

In this article, we describe a case of cerebral and cerebellar embolization with parenchymal seeding and high expression of IL-6 and MMP-2 after surgical resection of a left atrial myxoma. Moreover, we summarize a detailed review of the literature on intracranial embolization associated with parenchymal seeding, focusing on the potential pathogenic role of IL-6 and MMPs.

Correspondence: Joham Choque-Velasquez, MD, Department of Neurosurgery, Helsinki University Hospital, Topeliuksenkatu 5, 00260 Helsinki, Finland. Email: johchove@hotmail.com

Received 12 March 2020; revised 06 June 2020; accepted 12 June 2020.

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CLINICAL SUMMARY

A 69-year-old woman with a medical history of drug-resistant epilepsy for the past four months was admitted to the emergency service with acute left-side hemiparesis and distal tremor in both the hands. Ten months prior, she had undergone total excision of a sporadic left atrial myxoma at another institution. A deeper analysis of her medical history revealed repeated recurrent ischemic strokes several months before the heart surgery. No cardiac lesion was detected by echocardiography. Biochemical tests revealed high levels of C-reactive protein (4.3 mg/dL) and lactate dehydrogenase (538 U/L) in blood. Other tests, such as complete blood counts and metabolic panel, were normal.

Cranial computed tomography (CT) revealed cortical and subcortical hyperdense nodules surrounded by the vasogenic edema zone in the posterior fossa and cerebral hemispheres. Those lesions were predominantly located in the frontal, occipital, and cerebellar regions and were initially suspected as hemorrhagic events (Fig. 1). No magnetic resonance imaging (MRI) studies were performed due to unavailability of equipment. A stereotactic biopsy of the right occipital lesion was performed. The patient, with large and multiple intracranial lesions, died 30 months after initial cardiac surgery.

PATHOLOGICAL FINDINGS

The histologic findings showed brain parenchyma with hemorrhagic areas surrounded by abundant mucoid matrix containing sparse spindle-shaped or stellate cells. Tumor cells had oval nuclei and eosinophilic cytoplasm without nuclear pleomorphism or mitosis (Fig. 2). Immunohistochemical analyses confirmed parenchymal seeding of the myxoma cells with strong expression of calretinin (Fig. 3A). Multiple old hemorrhagic foci with clusters of hemosiderophages were also found. Based on these findings, we conclude a diagnosis of intracerebral embolization

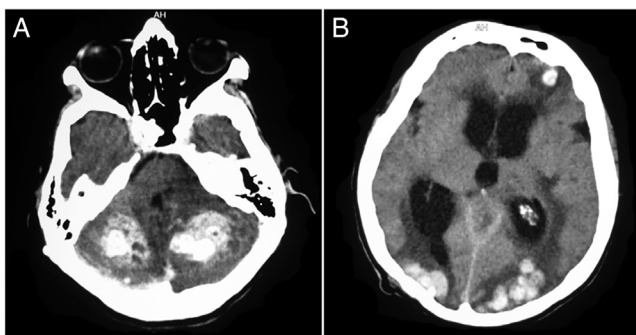


Fig. 1 CT findings of the brain. Axial images display multiple hyperdense nodules in cortical and subcortical regions of the cerebellum (A) and the frontal and occipital (B) lobes as well as subsequent hydrocephalus.

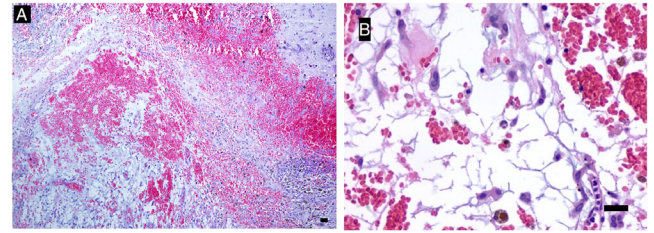


Fig. 2 Histological findings on the metastatic brain tumor biopsy specimen sections stained with HE. (A) The tumor shows abundant lepidic cells in a myxoid stroma infiltrating brain parenchyma in a bleeding background. (B) The tumor cells exhibit nuclear pleomorphism and mitotic figures (B). Scale bars: 100 μ m (A), 50 μ m (B).

of left atrial myxoma associated with large solid intraparenchymal lesions. Moreover, aiming to assess the role of the IL-6 and MMPs, we found high expressions of IL-6 (Fig. 3B), focal expression of MMP-2 (Fig. 3C), and negative expression of MMP-9 (Fig. 3D) in the tumor cells. Double immunohistochemical staining was initially planned. However, the lack of experience in our country prevented performing this procedure.

Review of original tissue sections of the surgically treated primary cardiac tumor revealed a left atrial myxoma with a papillary pattern, benign histological features, and uniform expression of calretinin into the myxoma cells (Fig. 4).¹⁵

DISCUSSION

We describe a patient with intracerebral embolization of left atrial myxoma associated with large parenchymal lesions. Here, we have confirmed that IL-6 and MMP-2 were expressed in intracranial embolic myxoma cells.

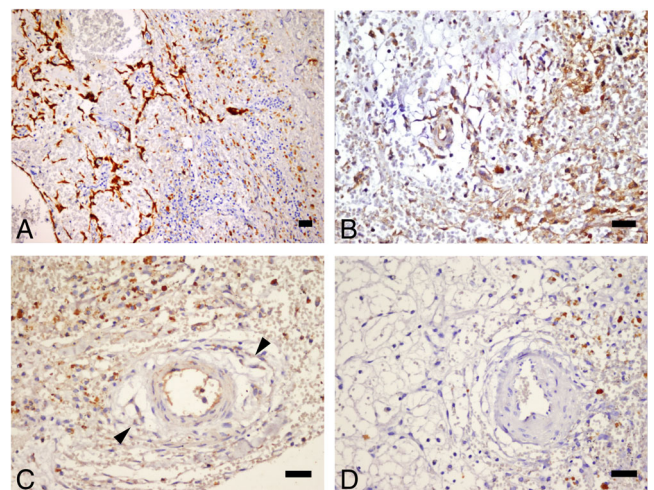


Fig. 3 Immunohistochemical observations on the metastatic brain tumor biopsy specimen sections stained for calretinin (A), IL-6 (B), MMP-2 (C), and MMP-9 (D). The tumor cells are immunoreactive for calretinin (A), IL-6 (B), and MMP-2 (C). MMP-9 immunoreactivity is detected only in inflammatory cells but undetectable in the tumor cells (D). Scale bars: 50 μ m (A-D).

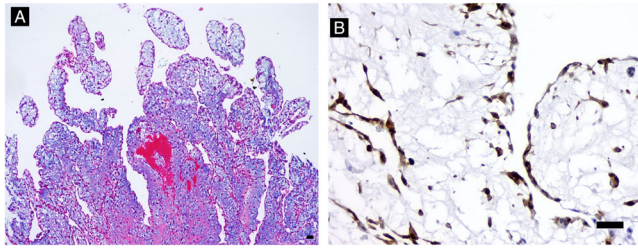


Fig. 4 Histological (A) and immunohistochemical (B) observations on the metastatic brain tumor biopsy specimen sections stained with HE (A) and immunostained for calretinin (B). At a low magnification, villous-type myxoma with numerous friable fronds is observed (A). At a higher magnification, myxoma cells are immunoreactive for calretinin (B). Scale bars: 250 μ m (A), 50 μ m (B). Scale bars: 250 μ m (A), 50 μ m (B).

Cardiac myxomas are benign tumors usually located in the left atrium and can embolize to several extracardiac tissues. Two gross subtypes of cardiac myxomas have been described: the solid type and the villous type. The villous-type tumors have an irregular, often friable, and papillary surface, as observed in our case. Immunohistochemical studies revealed uniform expression of calretinin in nearly all cardiac myxoma cases.¹⁵ The brain is the most frequent embolization site.¹ Neuroimaging studies have demonstrated that ischemic infarction events are the most frequent neurological findings (76.0–88.8%) in patients harboring left atrial myxomas with neurological manifestations.^{6,16} In contrast, the exact prevalence of late neurological complications in these patients is unknown because long-term studies evaluating the likelihood of delayed neurological complications have not been conducted. The largest single-center study, by Brinjikji *et al.*, in 47 patients treated for left atrial myxoma, reported that intracranial aneurysm and extravascular “metastasis” represented infrequent neuroimaging findings during the follow up of these patients (observed in 14.9% and 4.3% of cases, respectively).¹⁷ However, Zhang *et al.* followed 12 patients treated for left atrial myxoma with predominant neurological manifestations. They found that eight (67%) patients had multiple intracranial aneurysm, and that six (50%) patients exhibited extravascular “metastasis”.¹⁸

Although the mechanisms of embolization of a benign tumor and metastasis of an invasive malignancy are fundamentally different, the appearance of multiple lesions at a distant site in the setting of a cardiac myxoma has occasionally been referred to (erroneously) in the literature as “metastasis.”^{17,18} Since the first description made by Rankin *et al.*, in 1978,¹⁹ our comprehensive review revealed 36 histologically established cases of intracerebral embolization associated with parenchymal brain invasion from a benign left atrial myxoma (Table 1).^{10,14,18–51} A careful review of the cases confirmed that three patients have been reported twice,^{14,19,20,23,24,28} six patients had

unavailable histological proof,^{37,52–56} and four apparent primary cardiac sarcomas were erroneously reported as a cardiac myxoma.^{57–60} In one case, the original report could not be located,⁶¹ and another report described embolic myxoma cells in the leptomeninges without evidence of parenchymal seeding.⁶²

A summary of our review shows that cerebral embolization associated with parenchymal lesions usually occurs in adults of mean age of 47.6 ± 14.6 (range 15–70) years. There is a clear female predominance (male:female = 1:2). This rare condition might occur many years before, simultaneously with, or many years after the surgical excision of the primary tumor. Most patients (74.3%) developed intracerebral embolization several months after resection of the cardiac tumor (from 4 to 144 months), and in around 77.8%, multiple brain regions were involved. Left atrial myxomas preferentially lodge in the middle cerebral artery system.⁶³ Thus, parietal and occipital lobes are the most affected regions (91.6%). Moreover, the bone^{19,35,46} and the skin^{23,50} can be simultaneously involved. The most common clinical presentation of these patients was seizures (37.1%), followed by headache (31.4%), and hemiparesis (20%). However, unusual presentations such as gait disorders^{37,42,50} and visual disturbances^{25,27,43} have also been reported. In addition, the high frequency of intracranial aneurysms (75%) in these patients suggests that invasion and proliferation of myxoma cells into the vessel wall might represent a previous step to brain parenchymal seeding.

Although cerebral involvement occurred in almost half of patients with embolic events, it is currently suspected that only a small portion of distant embolic myxoma may progress to parenchymal seeding of tumor cells. No risk factors for the development of this rare complication are known, but previous history of multiple recurrent neurological symptoms associated with left atrial myxoma, such as multiple ischemic strokes or recurrent seizures, may increase the risk of their appearance. Indeed, up to 70.8% of patients with late-onset cerebral embolization associated with parenchymal seeding of the tumor cells presented with prominent neurologic symptoms during initial admission. This finding suggests that left atrial myxomas with previous history of multiple recurrent strokes are more likely to develop delayed neurological manifestations during follow up.^{10,17}

Despite multiple parenchymal seeding, the histology of the primary and embolic tumor infiltrates remains benign without evidence for malignant transformation. Histological evaluation of primary tumor frequently reveals benign cardiac myxomas with prominent papillary surface projections.^{19,24,29,49} Occasionally, cardiac myxofibrosarcomas⁶⁴ or metastatic adenocarcinomas^{10,30} might resemble cardiac myxomas. Based on these circumstances, calretinin

Table 1 Cerebral embolization associated with parenchymal seeding of the left atrial myxoma reported in the literature

| Year | Author | Age/ sex | Interval between myxoma surgery and embolization | Initial symptom of the disease | Clinical presentation of the embolism | Location | Aneurysm formation | Other embolisms | Treatment | Outcome | Survival |
|------|-------------------------|-------------|--|--|---|---------------------------|-----------------------|--------------------|-----------------|---------|-----------|
| 1978 | Rankin LI, Seo IS | 44 F | +96 months | Recurrent stroke | Hemiparesis, aphasia | Choroid plexus | NAD | Bone | Surgery | Alive | 72 months |
| 1979 | Budzilovich G | 52 F | Post-mortem | NAD | Death on arrival | P, cerebellum, dura | NAD | — | No | Death | NAD |
| 1987 | Bazin A | 56 F | +48 months | NAD | NAD | Cerebrum- cerebellum | NAD | — | Surgery | NAD | NAD |
| 1987 | Morimoto K, Kadota T | 44 M | +11 months | Recurrent stroke | Hemiparesis, seizures | F-P | NAD | Skin | Surgery | Alive | NAD |
| 1990 | Ng HK | 54 M | +4 months | NAD | Visual disturbances, seizures | O | NAD | — | Surgery | Alive | 24 months |
| 1992 | Chozick BS | 61 F | +8 months | Unspecific Hematuria | Seizures | F | No | — | Surgery | Alive | 84 months |
| 1993 | Chen HJ | 68 F | +12 months | | Headache, visual disturbances | O | Yes | — | Surgery | Alive | 24 months |
| 1993 | Wada A, Kanda T | 70 M | −9 months | Recurrent stroke | Hemiparesis | O | NAD | — | Surgery | Alive | 1 month |
| 1994 | Samaratunga H | 60 F | −7 months | Seizures | Seizures | P, dura | Yes | — | Surgery | Alive | 14 months |
| 1997 | Scarpelli M | 64 M | +144 months | NAD | Unspecific symptoms | P-O | NAD | — | Surgery | NAD | NAD |
| 2004 | Hirudayaraj P | 50 F | −1 month | Hemiparesis | Hemiparesis | P | NAD | — | Surgery | Alive | 24 months |
| 2005 | Altundang MB | 41 F | +15 months | Dyspnea | Seizures | F-P-O, cerebellum | NAD | — | Surgery + RT | Alive | 63 months |
| 2010 | Balasuriya BM | 30 F | +48 months | Seizures | Hemiparesis, seizures | F-O | Yes | — | NAD | NAD | NAD |
| 2006 | Rodrigues D | 65 M | +12 months | NAD | Hemiparesis, Seizures | P-O | NAD | — | Surgery | Alive | 72 months |
| 2006 | Rodriguez F | 41 F | −22 months | paresthesia / visual disturbance | Seizures, paresthesia | F-P-O | Yes | Bone | Surgery | Alive | 23 months |
| 2007 | Moiyadi AV | 35 M | −48 months | Seizures | Seizures | F-P-T-O | NAD | — | RT | Alive | 6 months |
| 2007 | Rabarijaona M | 53 F | +48 months | Seizures | Seizures | F-P-O, cerebellum | Yes | — | Surgery | Alive | NAD |
| 2008 | Wolf M | 60 M | +9 months | Palpitations | Seizures, hemiparesis | P-O, cerebellum | No | — | Conservative | Alive | 78 months |
| 2008 | Suzuki R | 68 M | +6 months | Stroke | Headache | Multiple | NAD | — | Surgery + RT | Alive | NAD |
| 2010 | Eddleman C | 18 M | +4 months | Dyspnea | Headache | O | Yes | — | Surgery | Alive | NAD |
| 2011 | Kumar A | 30 F | +24 months | Seizures | Seizures | F-P-O | Yes | — | Conservative | Alive | NAD |
| 2012 | Badriyah | 15 F | + 44 months | NAD | Headache | P-O | NAD | — | Surgery | Alive | 12 months |

(Continues)

Table 1 (Continued)

| Year | Author | Age/ sex | Interval between myxoma surgery and embolization | Initial symptom of the disease | Clinical presentation of the embolism | Location | Aneurysm formation | Other embolisms | Treatment | Outcome | Survival |
|------|---------------------|-------------|--|--------------------------------------|---|----------------------|-----------------------|--------------------|-----------------|---------|------------|
| 2012 | Radoi MP | 45 M | +18 months | NAD | Seizures, hemiparesis | F-P | Yes | — | Surgery | Alive | 12 months |
| 2013 | Rique J | 42 F | Simultaneous | amaurosis | Amaurosis | F-O | NAD | — | Surgery | NAD | NAD |
| 2015 | Côté I | 46 F | +24 months | Seizures | Seizure | F-P | No | — | Surgery | Alive | 12 months |
| 2016 | Castañón- Leon A | 40 F | −1 month | Dyspnea | Headache | F-P-O, cerebellum | Yes | — | Surgery + RT | Alive | NAD |
| 2017 | El Sabbagh | 41 F | −24 months | Headache, hemiparesis | Headache, hemiparesis | F | NAD | Bone | Surgery | NAD | NAD |
| 2017 | Ryu J | 43 F | +9 months | Stroke | Seizure | P | NAD | — | Surgery + RT | NAD | NAD |
| 2019 | Wan Y | 39 F | +7 months | NAD | Headache, visual disturbances | F-P-O | Yes | — | Surgery | Alive | 11 months |
| 2019 | Roque A | 48 F | −5 months | Headache | Headaches | F-P-O | Yes | — | RT | Alive | 18 months |
| 2019 | Zhang S | 49 F | +11 months | NAD | Headaches | P-O | Yes | — | NAD | Alive | 23 months |
| 2019 | | 16 F | +34 months | NAD | Hemiparesis | P-O | Yes | — | NAD | Alive | 113 months |
| 2019 | | 39 F | +8 months | NAD | Hemiparesis | P-O | Yes | — | NAD | Alive | 32 months |
| 2019 | | 39 F | +8 months | NAD | Headaches | P-O | No | — | NAD | Alive | 21 months |
| 2020 | Maas JA | 62 M | −3 months | Hemiparesis | Hemiparesis, blurred vision | F-P-O | NAD | Skin | Surgery | Alive | 48 months |
| 2020 | Panos | 63 M | +9 months | Stroke | Seizures | P-O | Yes | — | RT | Alive | 36 months |
| 2020 | Present case | 69 F | +10 months | Recurrent stroke | Seizures, distal tremor | F-P-O, cerebellum | NAD | — | Conservative | Death | 30 months |

immunohistochemistry is paramount for the proper identification of embolic cardiac myxomas. In our review, only seven of 36 cases evaluated calretinin expression in the infiltrative tumor cells.^{35,39,43,45,47,49}

Although the mechanism of the brain parenchymal seeding after complete local resection of cardiac myxomas has not been elucidated, embolic tumor cells might remain active and invade the wall of the distant vessels.^{29,35,39,45} Traditionally, the vasa vasorum has been considered a key element for the embolization of tumor particles. Thus, small particles entering in the vasa vasorum penetrate the subintimal tissue, leading to subsequent fragmentation of the arterial wall.^{42,45} However, this explanation seems incomplete because the existence of vasa vasorum has only been demonstrated in proximal intracerebral arteries,^{65,66} and most cerebral emboli occur predominately in distal intracerebral arteries.^{6,42,45,67} In contrast, some authors suggest that the viable tumor particles may cause progressive disruption of the internal elastic lamina through a direct transendothelial invasion rather than hematogenous seeding via vasa vasorum.^{21,45} Several histological studies have demonstrated that proliferation of myxoma cells in the arterial wall^{29,35,39,45} behave like a nidus for aneurysm formation and an anchor for subsequent growth of the extravascular tumor tissue.

The mechanisms by which cardiac myxoma cells penetrate the cerebral vessel wall remain unknown. Some authors have proposed that IL-6 produced by cardiac myxoma may play a crucial role in the adhesiveness of myxoma cells to cerebral vascular endothelial cells, through the induction of intercellular adhesion molecule-1 (ICAM-1) during intracerebral embolization.¹⁴ In addition, Yaguchi *et al.*⁶⁸ reported an isolated increase in IL-6 levels in cerebrospinal fluid (CSF), in contrast to normal serum levels, in a patient with multiple newly formed intracranial aneurysms after resection of a cardiac myxoma. These findings suggest that the high level of IL-6 in CSF reflects overproduction of IL-6 by embolic myxoma cells in the intracranial vessel. In light of these previous hypotheses,^{14,67–69} we are reporting for the first time the direct evidence for IL-6 expression in embolic tumor cells of a left atrial myxoma within brain parenchyma.

Increased systemic and local production of IL-6 has been reported in patients with cerebral aneurysms associated with cardiac myxomas.^{14,67–69} IL-6 stimulates the gene expression of some MMPs, including MMP-2 and MMP-9, via the activator protein-1 pathway.⁷⁰ MMP-9 is known to break the blood–brain barrier and probably to facilitate the CNS invasion of myxoma cells.⁷¹ Cultured cells of the embolic myxomas treated with IL-6 had a higher increase in the activity of both MMP-2 and MMP-9 than cells from non-embolic myxomas.⁷² The proteolytic role of MMPs in expansion of trophoblasts

and cancer cells is well described.^{73,74} Among the MMP superfamily, MMP-2 and MMP-9 are essential for the fragmentation of the internal elastic lamina in both clinical and experimental model studies.^{75–77} In the present case, we could demonstrate the expression of MMP-2 in infiltrative myxoma cells. This finding might suggest that MMP-2 play a more sustainable role in brain parenchymal seeding of myxoma cells than MMP-9.^{78,79}

Since the first resection of a cardiac myxoma in 1953, the standard treatment of these tumors has been surgical removal to reduce the rate of embolic events.⁸⁰ In contrast, the standard management of intracerebral embolization after resection of the primary cardiac tumor has not been well established due to its rarity and variable clinical course. In our review, similar to the primary cardiac tumor, surgery was the most frequent therapeutic option in patients with accessible brain lesions. Radiotherapy has been frequently conducted for patients with multiple or progressive lesions, with promising results, although clinical follow up managements are limited.^{10,32,38,45,47,49,51} Considering that these lesions have persistently active tumor cells, adjuvant chemotherapy would be a reliable option to reduce the risk of extracardiac seeding. However, no previous information on experiences in the management of this therapeutic option in cardiac myxomas is available. Currently, surgical resection associated with radiotherapy is widely used to stabilize the progressive neurological complications in these patients.^{32,38,45,47}

Further research is still required to understand the behavior of left atrial myxoma. However, careful attention should be paid to the neurological symptoms of the patients to detect delayed neurological complications. With complete surgical resection of the cardiac myxoma, strict follow up of the patients should still occur.

Although the left atrial myxoma is a benign tumor, it has the potential to embolize, especially in the brain. Cerebral embolization associated with progressive parenchymal seeding of the tumor is an extremely rare complication that may occur several years after surgical removal of the primary cardiac tumor. The appearance of recurrent neurological symptoms during the clinical course of left atrial myxoma may be a risk factor for late-onset neurological manifestations. Our case supports previous observations that the expression of IL-6 and MMP-2 in myxoma cells favors progression of the intracranial embolic process. Thus, future research is essential to determine the diagnostic and therapeutic application of these markers for the tumor.

ACKNOWLEDGMENTS

None.

DISCLOSURE

The authors have no personal financial or institutional interest in any of the drugs, materials, and devices described in this article.

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